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CLINICAL INVESTIGATION **Genitourinary Cancer**

PROSTATE SPECIFIC ANTIGEN BOUNCE IS RELATED TO OVERALL SURVIVAL IN PROSTATE BRACHYTHERAPY

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Purpose: To investigate the association between prostate specific antigen (PSA) bounce and disease outcome after prostate brachytherapy.

Methods and Materials: We analyzed 975 patients treated with ^{125}I implantation monotherapy between 1992 and 2006. All patients had tumor Stage ≤2c, Gleason score ≤7 prostate cancer, a minimum follow-up of 2 years with at least four PSA measurements, and no biochemical failure in the first 2 years. Median follow-up was 6 years. Bounce was defined as a PSA elevation of +0.2 ng/mL with subsequent decrease to previous nadir. We used the Phoenix +2 ng/mL definition for biochemical failure. Additional endpoints were disease-specific and overall survival. Multivariate Cox regression analysis was performed to adjust for potential confounding factors.

Results: Bounce occurred in 32% of patients, with a median time to bounce of 1.6 years. More than 90% of bounces took place in the first 3 years after treatment and had disappeared within 2 years of onset. Ten-year freedom from biochemical failure, disease-specific survival, and overall survival rates were, respectively, 90%, 99%, and 88% for the bounce group and 70%, 93%, and 82% for the no-bounce group. Only 1 patient (0.3%) died of prostate cancer in the bounce group, compared with 40 patients (6.1%) in the no-bounce group. Adjusted for confounding, a 70% biochemical failure risk reduction was observed for patients experiencing a bounce (hazard ratio 0.31; 95% confidence interval 0.20–0.48).

Conclusions: A PSA bounce after prostate brachytherapy is strongly related to better outcome in terms of biochemical failure, disease-specific survival, and overall survival.

Bounce, PSA spike, Transient PSA elevation, Brachytherapy, Prostate cancer.

INTRODUCTION

Prostate specific antigen (PSA) levels after definitive treatment for prostate cancer are an important source of information concerning disease status and treatment success. After any form of radiation treatment, a steady decline of serum PSA can be observed until usually a low level remains. A subsequent rise of PSA generally is suggestive of disease recurrence and, if the increase exceeds 2 ng/mL, is termed *biochemical failure* (BF) (1). However, in up to 40% of patients treated with a form of radiotherapy (2), a transient rise in PSA levels is observed, without apparent disease recurrence and with subsequent normalization of PSA values. This is called a *PSA bounce*.

To date, no conclusive evidence-based explanation for the bouncing behavior of PSA exists. Precipitating factors such as ejaculations or instrumentation are known to cause some PSA fluctuation (3), and the physiologic variability of PSA assays in healthy test subjects was found to be considerable (4). A small fraction of bounces may be caused by such factors; however, they fail to provide a complete explanation.

For prostate brachytherapy, recent studies concluded that the occurrence of a PSA bounce was related to increased freedom from BF, which can not be explained by any of the above mechanisms (5, 6). However, other studies did not find the same association (7, 8). These inconsistent results might be caused by several factors, such as differences in isotopes used (9), a difference in bounce definition, and different selection criteria.

More importantly, however, until now outcome for studies on bounce and brachytherapy have only been reported as BF,

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and no study has reported on disease-specific and overall survival in relation to bounce.

If indeed bounce is related to improved outcome after brachytherapy, the occurrence of a bounce will be an important indicator in follow-up and may even become a parameter of treatment success. Therefore, the purpose of this study was to determine the association between bounce and disease outcome after prostate brachytherapy, as BF but also as disease-specific and overall survival, in a large prostate cancer brachytherapy cohort.

METHODS AND MATERIALS

The study population consisted of patients with locally confined prostate cancer, treated with ^{125}I brachytherapy between 1992 and September 2006 at the Department of Radiotherapy, University Medical Center Utrecht, in the Netherlands. Clinical information of all patients treated in this period was prospectively recorded in a database. Study selection criteria included a minimum of four available PSA determinations, at least 2 years of follow-up, no prostate cancer–related supplementary surgery or external-beam radiotherapy, and no BF in these first 2 years. The final analysis was performed on a total of 975 patients. The ^{125}I implantation procedure was based on a transrectal ultrasound–guided approach, with a planned total dose of 144 Gy (10). Both stranded seed as well as loose seed implants were used interchangeably. From 1998, routine volume studies and preplanning were performed in all patients, and three-dimensional (3D) ultrasound–based intraoperative planning was introduced in 2000. Starting in 2003, patients received preimplant MRI scans, which could be fused with 3D ultrasound to facilitate intraoperative prostate delineation. The implantation technique and procedure have been described in more detail in previous work (11, 12). Patients with a prostate volume exceeding 50 cm^3 received 6 months of preimplant androgen deprivation therapy to downsize the prostate for implantation feasibility. Androgen deprivation therapy consisted of a luteinizing hormone-releasing hormone agonist.

Our primary endpoint was BF, according to the Phoenix definition (+2 ng/mL rise of PSA above nadir) (1). Our secondary endpoints were disease-specific survival and overall survival. The follow-up consisted of visits every 3 months during the first year and half-yearly visits thereafter, at which point PSA levels were determined. Date of death was established through the national population registry, and cause of death was determined by contacting the related general practitioner or by means of the hospital information system. Death with distant metastasis was considered as death from disease.

Different bounce definitions exist (2), with different threshold values, typically in the range of +0.1 ng/mL to +0.5 ng/mL. We report our results according to the +0.2 ng/mL definition, which is the most widely used bounce threshold in literature. To investigate the impact of a higher bounce threshold on our results, we performed an additional sensitivity analysis with the +0.5 ng/mL threshold definition.

In addition, our bounce definition included a normalization of PSA values to or below previous nadir. We defined no time span for bounce occurrence.

Risk stratification was performed according to Ash *et al.* (13). Thus, defining low risk as maximum tumor (T) Stage 2a, Gleason score 6, and initial PSA level <10 ng/mL. Intermediate risk was defined as either T Stage 2b/2c, Gleason score 7, or initial PSA level 10–20 ng/mL combined with two low-risk features. High risk was defined as two or three intermediate-risk factors or initial PSA level >20 ng/mL. Tumor staging was based on the 2002 version of the American Joint Committee on Cancer system.

Baseline characteristics were reported as means ± SD, medians with interquartile range (IQR), or as percentages. The associations between the occurrence of bounce and clinical as well as pathologic data were examined with Student's *t*-test for parametric variables and with the Mann-Whitney test in case of categoric or nominal variables. The Kaplan-Meier method was used for comparing patients with or without a bounce and the time to the defined

Table 1. Baseline characteristics of the study patients divided by bounce occurrence

Baseline characteristics	Bounce	No bounce	*p*	Total
Patients (*n*)	314	661		975
Age (y)	64 ± 6.5	67 ± 6.4	<0.001	66 ± 6.6
PSA at diagnosis	7.7 (5.6–11.0)	9.1 (6.3–13.3)	<0.001	8.6 (6.0–12.2)
Tumor stage			<0.001	
≤2A	290 (92)	562 (85)		852 (87)
≥2B	24 (8)	99 (15)		123 (13)
Gleason score			0.024	
<7	169 (54)	301 (46)		470 (48)
7	142 (46)	360 (54)		502 (52)
Risk class			<0.001	
Low	107 (34)	155 (24)		262 (27)
Intermediate	146 (47)	281 (43)		427 (44)
High	58 (19)	221 (34)		279 (29)
Androgen deprivation therapy	63 (20)	118 (18)	ns	181 (19)
Transurethral prostate resection	26 (8)	61 (9)	ns	87 (9)
Prostate volume (cm^3)	36 ± 10.8	35 ± 11.6	ns	35 ± 11.4
Seeds implanted	73 ± 16.3	70 ± 18	<0.001	71 ± 17.6
Follow-up (y)	6.2 (4.5–8.0)	5.8 (4.3–8.2)	ns	6.0 (4.4–8.1)
No. of PSA measurements	9 (7–12)	7 (5–10)	<0.001	8 (6–11)
D90 at implantation* (n = 142)	155 (134–178)	162 (139–180)	ns	159 (137–179)

Abbreviations: IQR = interquartile range; PSA = prostate specific antigen; D90 = minimal delivered dose (in Gy) to 90% of the prostate volume, as measured 4 weeks after implantation.

Values are mean ± SD, median (IQR), or number (percentage).

* Dosimetry was only available since the end of 2004.

endpoints. The difference in time-adjusted incidence rates was compared with the log–rank test for censored data.

To adjust for baseline differences and potential confounding factors, univariate and multivariate Cox proportional hazards regression analyses were performed. Considered potential confounding factors were age, prebrachytherapy androgen deprivation therapy, prior transurethral prostate resection, the number of implanted seeds, prostate volume, treatment year, and prostate cancer risk class. The variables T stage, PSA at diagnosis, and Gleason score all are represented in the risk-group variable and were therefore omitted. According to the multivariate Cox proportional hazards regression model, in which at each time point an estimation of the risk, adjusted for baseline differences is calculated, figures were plotted to observe the independent effect of bounce. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated, and statistical significance was considered if $p < 0.05$. All analyses were performed with the Statistical Package for Social Sciences, version 16.0.2 (SPPS, Chicago, IL).

RESULTS

Baseline characteristics are presented in Table 1, subdivided into 314 patients with a bounce (32%) and 661 without a bounce (68%). In general, patients in the bounce group were younger and more often had low-risk prostate cancer. There was no difference in follow-up, with a mean follow-up of 6.5 years (range 2.3–17.9 years); approximately one third of the total patient population was treated in the previous decade and therefore had more than 10 years of follow-up. The median PSA bounce peak was 1.7 ng/mL (IQR 1.0–2.8). Forty-seven patients (4.8%) had a bounce peak exceeding the BF definition. The median time to bounce was 1.6 years (IQR 1.0–2.0 years), and more than 90% of bounces occurred in the first 3 years after implantation. The median bounce duration, defined as the time between onset of bounce and return to nadir, was 1 year (IQR 0.5–1.25 years), with more than 90% of bounces having disappeared in less than 2 years from onset.

We observed 24 patients with a BF in the bounce group (7.6%) vs. 181 (27.4%) in the no-bounce group. In the bounce group only 1 patient (0.3%) died of prostate cancer, compared with 40 patients (6.1%) in the no-bounce group. Figure 1 shows the Kaplan-Meier curve for freedom from BF for patients with and without a bounce. The log–rank tests for bounce and BF, disease-specific survival, and overall survival were all statistically significant ($p < 0.01$).

Univariate Cox proportional hazards regression for bounce and BF showed an HR of 0.22 (95% CI 0.14–0.34). After adjusting for potential confounders, the multivariate Cox proportional hazards model still provided a 69% BF risk reduction for patients with a bounce (HR 0.31; 95% CI 0.20–0.48). Results are shown in Table 2. Figures 2–4 show the corresponding Cox proportional hazards curves (adjusted for confounders) for bounce and, respectively, freedom from BF, disease-specific survival, and overall survival. The accompanying 10-year rates for freedom from BF, disease-specific survival, and overall survival were, respectively, 90%, 99%, and 88% for the bounce group and 70%, 93%, and 82% for the no-bounce group.

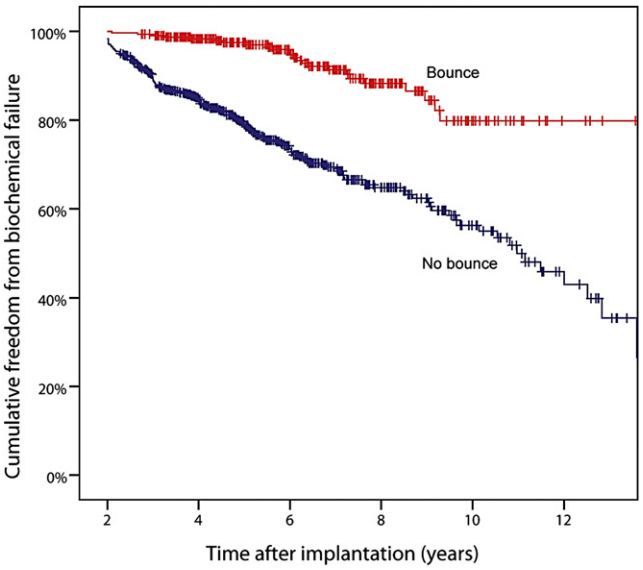

Fig. 1. Kaplan-Meier curve for prostate-specific antigen bounce and freedom from biochemical failure.

When substituting the +0.2-ng/mL for the +0.5-ng/mL bounce threshold, the bounce rate changed from 32% to 24%. The HR (adjusted for confounders) of bounce and BF changed slightly to 0.34 (95% CI 0.21–0.55). The 10-year rates for freedom from BF, disease-specific survival, and overall survival also changed marginally (data not shown), with log–rank tests remaining significant ($p < 0.01$).

DISCUSSION

The presented data show a very strong association between the occurrence of a PSA bounce and BF. Adjusted for potential confounding factors, a near 70% BF risk reduction is observed for patients experiencing a bounce after brachytherapy compared with patients without a bounce. Even more importantly, a significant association was found between bounce and death from disease, with only 1 patient (0.3%) dead of prostate cancer in the bounce group, compared with 40 patients (6.1%) in the no-bounce group.

Table 2. Multivariate Cox regression analysis of bounce and biochemical failure, adjusted for baseline differences

Variable	Hazard ratio	95% confidence interval	*p*
Age	1.01	0.99–1.03	ns
Androgen deprivation therapy	0.90	0.59–1.36	ns
Seeds implanted	1.01	1.00–1.02	ns
Prostate volume (cm^3)	0.98	0.97–1.00	ns
Year of treatment	0.88	0.83–0.93	<0.01
Risk class			
Intermediate	2.74	1.62–4.65	<0.01
High	5.96	3.60–9.86	<0.01
Bounce	0.31	0.20–0.48	<0.01

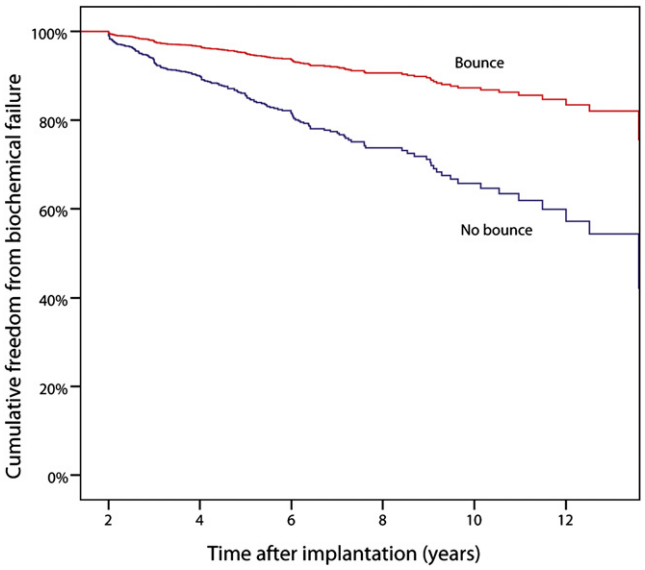

Fig. 2. Multivariate Cox regression curve for prostate-specific antigen bounce and freedom from biochemical failure, adjusted for baseline differences.

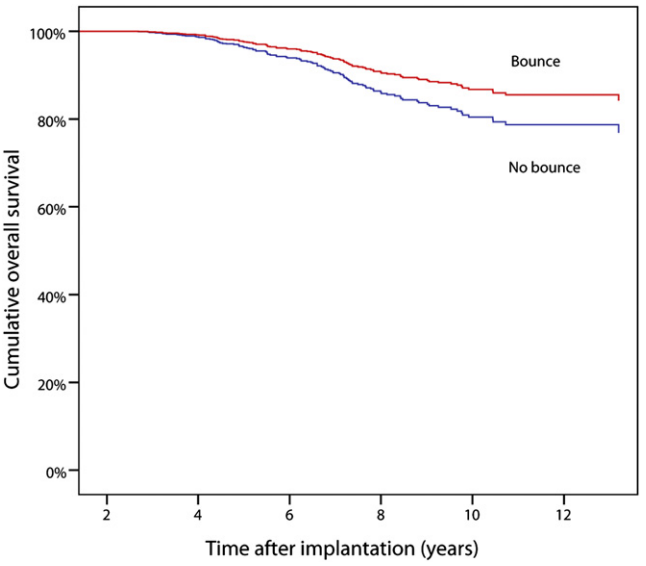

Fig. 4. Multivariate Cox regression curve for prostate-specific antigen bounce and overall survival, adjusted for baseline differences.

The poor performance of the high-risk patient group has in part influenced the low outcome of the no-bounce group; however, large differences still exist between the bounce and no-bounce group, as was calculated with the multivariate Cox regression analysis. The overall BF, disease-specific survival, and overall survival rates have been previously described (12), and for low- and intermediate-risk patients, outcomes are comparable to data from the literature. High-risk subgroup comparison is more difficult owing to its large heterogeneity and the resulting composition differences between studies.

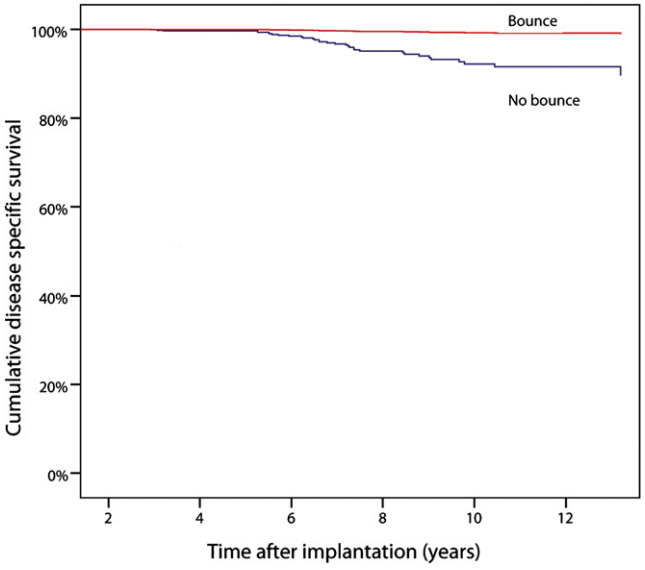

Fig. 3. Multivariate Cox regression curve for prostate-specific antigen bounce and disease-specific survival, adjusted for baseline differences.

Furthermore, it must be taken into account that the outcomes of this study are partly based on a patient population treated 2 decades ago. The results of patients treated in the last decade have much improved (12) owing to, for example, increased diagnostic accuracy, improved implant quality, and dosimetric quality control. This can also be seen in Table 2, where treatment year is a strong independent predictor of outcome. Nonetheless, most important is to note that the difference in outcome between the bounce and no-bounce group is independent of risk group, age, or treatment period.

After careful consideration, we decided to exclude from analysis patients with a disease recurrence in the first 2 years after treatment. These patients by definition have no chance to bounce and subsequently bias the outcome. All patients analyzed in our study had at least four PSA determinations with a minimum follow-up of 2 years, thus providing an equal chance to bounce for all patients. Indeed, up to 75% of patients bounced in those first 2 years. However, when extrapolating our results to the general patient population, that includes patients with early BF, the difference in prognosis between patients with or without a bounce would even be much larger. When defining a cutoff value for bounce, it is essential to choose a sensitive value, higher than the interassay variation. In the literature, the interassay mean coefficient of variation, specifically for a PSA <2 ng/mL, was reported to be approximately 2.8% for patients without prostate cancer (14). In addition, the general day-to-day variation of PSA assays at our in-house laboratory, where the majority of assays has been performed, was ascertained at 5–7%. To conclude, a +0.2-ng/mL definition for bounce seems suitable to differentiate bounce from test variations. Nevertheless, we repeated our calculations with the various bounce thresholds found in the literature, ranging from +0.2 ng/mL to +0.5 ng/mL. The differences in outcome between

definitions proved to be marginal and resulted in the same conclusions concerning the relation of bounce and outcome.

The bounce phenomenon can be observed after both brachytherapy as well as external-beam radiotherapy. However, we chose only to include brachytherapy studies in our literature overview because of differences between either treatment, such as the higher effective dose to the prostate, dose inhomogeneity, and a suggested higher bounce rate in brachytherapy (7, 15).

Three previous studies (5–7) reported on bounce and brachytherapy as monotherapy. The study of Patel *et al.* (5) and the more recent study from the same center by Ciezki *et al.* (6) also observed an improved BF outcome for patients experiencing a bounce. Ciezki *et al.* (6) (n = 162) used the same BF and bounce definition and had follow-up comparable to that in the present study. They did report a somewhat higher bounce rate of 46% and chose a minimum PSA follow-up period of 5 years. In contrast, Stock *et al.* (7) (n = 373) used various bounce definitions, with none showing an association between bounce and BF. Follow-up was shorter, and a number of patients received ^{103}Pd sources, and a difference in isotope has been previously shown to affect bounce occurrence (8).

The studies of Cavanagh *et al.* (16) and Critz *et al.* (17) reported on a combination of brachytherapy with external-beam radiotherapy. Cavanagh *et al.* (16) (n = 591) did not find an association between bounce and BF. In the study of Critz *et al.* (17) (n = 1011), a significant association between bounce and BF rate was found. However, the authors concluded that this was a biased result due to inclusion of patients with early BF; unfortunately, no additional analyses to overcome this bias were performed. Although follow-up was comparable to that in the present study, different bounce (+0.1 ng/mL) and BF definitions were used. This affects the bounce likelihood and could also have influenced the study outcome. Furthermore, the use of external-beam radiotherapy limits the comparability with the present study.

Strengths of our study include, among others, the addition of the secondary endpoints disease-specific survival and overall survival. None of the above-mentioned studies reported on these endpoints.

Although BF is generally considered a reasonable surrogate outcome for prostate cancer–specific mortality (18), death due to prostate cancer remains the more relevant clinical endpoint. Unlike BF, disease-specific survival is less susceptible to loss to follow-up because of the possibility to ascertain death and cause of death retrospectively through hospital information systems and national registries. Additionally, BF is more prone to information bias (i.e., potential dissimilarities in PSA testing frequency during follow-up could affect the diagnosis of BF). Moreover, the lack of uniformity in BF definitions through time makes it much more difficult to compare studies with a difference in BF definition.

Limitations of our study include the partial availability of dose parameters. These parameters were calculated onward from the end of 2004 and could therefore not be accounted for in our main analyses. The value of dosimetry has only been established in the last decade and therefore is unavailable when analyzing long-term data that are necessary for calculating overall and disease-specific survival. Nonetheless, in 144 patients dosimetry was available, and for this subset no association between dose and bounce occurrence could be established. Follow-up was too short for subanalysis of bounce and BF in these 144 patients. External validation of our findings in a ^{125}I brachytherapy cohort with extensive follow-up for patients with dosimetric data will be required to investigate whether the received dose influences the bounce occurrence and whether a lower implant quality can partly account for the worse outcome seen in patients without a bounce.

Patients in the bounce group had a slightly higher PSA testing frequency, probably due to increased follow-up intensity, although duration of follow-up was equal in both groups.

Prostate-specific antigen bounces are an important problem for both clinicians and patients because of BF false calls. This results in unnecessary anxiety in patients and a treatment dilemma for doctors. Our results confirm that the average bounce occurs earlier than BF; 90% of bounces occurred in the first 3 years, although considerable overlap exists. In the entire cohort of our brachytherapy patients, the risk of a BF false call was <5%, and most bounces had disappeared within 2 years. The mechanism behind the bounce phenomenon is still unknown. Different hypotheses are mentioned in the literature, but no evidence-based explanation exists to date. It is supposed that bounce may primarily be a delayed radiation effect on remaining prostate tissue (19). This hypothesis was based on the time frame of bounce occurrence coinciding with late urinary symptoms at 1 to 2 years after treatment. However, a recent publication from our center on health-related quality of life in brachytherapy patients showed a near-baseline resolution of urinary symptoms within the first year (20). In a second theory, Akyol *et al.* (2) describe the relationship between rising testosterone levels and bounce occurrence, after a combination of external-beam radiotherapy and short-term androgen deprivation therapy. Not only the androgen deprivation therapy itself but also supposed radiation effects (e.g., due to scatter on the testicles) were hypothesized to influence testosterone kinetics and consequently result in PSA bouncing (2). Although in our study only approximately 20% of patients received androgen deprivation therapy before treatment, its use was as common in both the bounce and no-bounce group, and we could not confirm a relation between androgen deprivation therapy and bounce occurrence.

A third hypothesis points out that sexual activity and prostate instrumentation have a large impact on PSA fluctuations and may be a cause of bounce (3). A slightly younger age is seen throughout literature for patients with a bounce compared with patients without a bounce; perhaps higher sexual activity can account for the higher frequency of younger age in the bounce group. The above-mentioned factors will undeniably have some influence on PSA variation; and it is known that the physiologic variability of PSA assays in healthy individuals is substantial (4). However, none of the

above-mentioned hypotheses can explain why bounce is found to be related to better survival. Rosser *et al.* (21) proposed that a PSA bounce may be caused by the physiologic response of prostate tissue to radiation, with a transition of sublethal to lethal cellular damage resulting in en-mass cell death and a sudden release of high PSA levels into the bloodstream. Consequently, the absence of bounce may suggest a lesser treatment effect with possibly a more malignant cell line that is less responsive to radiation. Although this hypothesis matches our findings, it will have to be supported by future evidence.

In a recent study by Kirilova *et al.* (22) patients with a bounce after ^{125}I brachytherapy were examined using 3D MR spectroscopy. They found that an ordinary bounce was accompanied by diffuse metabolic activity that was not related to residual malignancy, whereas in case of recurrence more focal activity was observed. Consequently, it was proposed that in certain cases 3D MR spectroscopy might be used to help clinicians differentiate true bounce from early disease recurrence.

To conclude, although the bounce phenomenon is clearly not yet properly understood and may in part be contaminated because of other causes of PSA fluctuation, a significant and clinically relevant relation was seen between bounce occurrence and disease outcome after prostate brachytherapy.

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